DETAILED ACTION

1. Acknowledgement of the amendment filed 11/15/2007 is made.

Response to Arguments

2. Applicant's arguments filed 11/15/2007 have been fully considered but they are not persuasive.

3. Regarding Applicants' arguments with respect to the rejection of claims under 35 U.S.C. 102(b) based on Lang, Applicants argue that Lang does not teach "a method of monitoring the accumulation of a compound of interest at a desired site in vivo by MRI, wherein there is increased blood flow to the desired site" (para 2 of page 15 in the Arguments filed 11/15/2007). However, Examiner points out that Lang does teach administering the liposome composition to a tumor site, or sites with increased capillary permeability (col. 1, lines 46-49; col. 2, lines 59-65). Examiner asserts that this would satisfy the limitation "wherein there is increased blood flow to the desired site" because Lang clearly teaches that the targeted drug delivery sites are those with increased capillary permeability, which would result in increased blood flow. Applicants also argue that Lang does not teach "a method of detecting an in vivo blood pool" (para 3 of page 15 in the Arguments filed 11/15/2007). Examiner asserts that Lang does teach detecting a blood pool since the liposome composition targets tumor areas and are readily visible in the MRI scan, thereby detecting a blood pool for the operator via an enhanced contrast signal (see col. 9, lines 52-55).

4. Regarding Applicants' arguments with respect to the rejection of claims under 35 U.S.C. 103(a) based on Lang in view of Fenn, Applicants argue that Lang and Fenn do not teach "an envirosensitive liposome nor demonstrate the ability to monitor drug distribution" (para 3 of page 17 in the Arguments filed 11/15/2007). However, Examiner asserts that Lang does teach the limitation regarding drug distribution (at least in the abstract). Regarding the limitation of an envirosensitive liposome, Examiner directs Applicants' attention to pages 3 and 4 of the Office Action filed 10/23/2006, where Examiner has explained how Fenn teach using thermo-sensitive liposomes for drug delivery and the obvious advantage that one of ordinary skill in the art would recognize. Applicants also argue that Lang and Fenn do not teach or suggest "an in vivo method of monitoring the localization and distribution or the accumulation of a compound of interest, where in the monitoring is performed as the compound of interest is being released from the envirosensitive liposome at the desired site". However, Examiner asserts that Lang in combination with Fenn clearly teach these limitation. Specifically, Lang teaches the monitoring of the compound of interest via MRI (abstract of Lang), while Fenn teaches releasing the compound of interest at a desired site with focused radiation to release the compound of interest at the desired site (abstract of Fenn). Again, Examiner directs Applicants' attention to pages 3 and 4 of the Office Action filed 10/23/2006, where Examiner has explained how Fenn teach using thermo-sensitive liposomes for drug delivery and the obvious advantage that one of ordinary skill in the art would recognize.

5. Regarding Applicants' arguments with respect to the rejection of claims under 35 U.S.C. 103(a) based on Lang in view of Fenn and further in view of Unger '319, Applicants argue that Unger '319 does not teach a subject that is "tantamount to using ultrasound to heat a desired site in vivo such that the accumulation and distribution of a liposome encapsulated compound of interest can be monitored via MRI". However, Examiner emphasizes that Unger '319 is used to show that ultrasound radiation can be used to heat a site, as Lang and Fenn already teach using thermosensitive liposomes for drug delivery, obviating any need for Unger '319 to teach anything more than the use of ultrasound as a method of heating a site to activate a site in vivo. Applicants also argue that "the combination does not disclose a method of generating a heating profile of a site of interest". However, Examiner asserts that generating this heating profile would be inherent and necessary whether the ultrasound is used to heat a tumor or a site of interest to activate thermosensitive liposomes (this may also be a tumor site as disclosed in Para [0006] of the instant application).

6. Regarding Applicants' arguments with respect to the rejection of claims under 35 U.S.C. 103(a) based on Lang in view of Fenn, further in view of Unger '319 and further in view of Unger et al. '935, Applicants argue that there is "no teaching in Unger et al. '935 of liposome formulations comprising DPPC-DSPE-PEG_{2000} or DPPC-MSPC-DSPE-PEG_{2000}". However, Examiner directs Applicants' attention the last paragraph of page 4 of the Office Action dated 10/23/2006, where Examiner has already explained how Unger '935 teaches the

DPPC-PEG formulation in col. 19, lines 24-39 which would make it obvious to one of ordinary skill in the art to use the formulation listed by Applicants.

7. Regarding Applicants' arguments with respect to the rejection of claims under 35 U.S.C. 103(a) based on Lang in view of Gamble et al., Applicants argue that Gamble et al. do not teach the deficiencies of Lang. However, as explained above, the deficiencies contended by Applicants have already been taught by Lang.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. **Claims 1, 4, 6, 7, 19, 20, 25-28, and 42** are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Lang (WO 98/44910). Lang '910 discloses a method of monitoring the drug delivery to a tumor (pg 5, L3-5), the method comprising:

(a) administering to a subject a non-sensitive liposome composition comprising:

(i) a contrast agent (pg 5, L7-8), wherein the contrast agent comprises an element selected from the group consisting of Gd (pg 3, L7 & 11);

(ii) a therapeutic agent (pg 5, L14-15), wherein the therapeutic agent is a chemotherapeutic agent (pg 7, L8-16); and

(iii) a non-sensitive liposome encapsulating the contrast agent and the compound of interest (pg 5, L9-15); and

(b) monitoring the accumulation of the compound of interest at the tumor site

by magnetic resonance imaging (pg 5, L16; pg 5, L3-5; By monitoring via MRI imaging, the operator would be able to visually examine differences in pixel densities.).

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. **Claims 8, 12, 13, 15-18, 22, 23, 29-31, 33, 34, and 46** are rejected under 35 U.S.C. 103(a) as being unpatentable over Fenn (U.S. 5,810,888). Lang '910 discloses all of the limitations as discussed above. Lang '910 does not disclose the use of a thermo-sensitive liposome for drug delivery. Fenn '888 teaches the use of a thermo-sensitive liposome for drug delivery by transmitting electromagnetic radiation to the site of interest wherein the liposome contains chemotherapy agents (C17, Claim 15-17, the thermal breakdown of thermo-

sensitive liposomes would release the contrast agent disclosed by Lang '910). Fenn '888 also discloses the possibility of using medical imaging modalities such as Magnetic Resonance Imaging to detected the temperature of the site while heating (C9, L21-27). It would have been obvious to a person of ordinary skill in the art to modify Lang '910 to include the use of a thermo-sensitive liposome in the method of drug delivery and monitoring as evidenced by Fenn '888. Such a modification would increase the concentration of a drug within the tumor during drug delivery (C2, L19-22).

12. **Claims 3, 9-11, 35, and 37-40** are rejected under 35 U.S.C. 103(a) as being unpatentable over Lang '910 in view of Fenn '888, and further in view of Unger (U.S. 5,149,319). Lang '910 and Fenn '888 disclose all of the limitations as discussed above. Lang '910 does not disclose the use of ultrasound to heat the tumor site. However, Unger '319 teaches the use of ultrasound to heat the tumor site (C1, L54-58). It would have been obvious to a person of ordinary skill in the art at the time of the invention to modify Lang '910 to include the use of ultrasound to heat the tumor site as evidenced by Unger '319. Such a modification would be advantageous by causing tumor cells to die and eventually destroying the tumor (C1, L24-31, by heating the site of interest, blood flow is also increased).

13. **Claims 14, 24, 32, 36, 41, and 43-45** are rejected under 35 U.S.C. 103(a) as being unpatentable over Lang '910 in view of Fenn '888, further in view of Unger '319, and further in view of Unger et al. (U.S. 5,542,935).

Regarding **claims 14, 24, 32, and 36,** all the limitations are disclosed as discussed above. None of the references described except for Unger '935 discloses a particular formulation of a thermo-sensitive liposome. Unger '935 discloses many different formulations of liposomes, including DPPC-PEG (C19, L24-39). It would have been obvious to a person of ordinary skill in the art to use a thermo-sensitive liposome comprising a formulation of PEG and DPPC. Liposomes are often liked to polymers of polyethylene glycol in order to achieve greater stability (C19, L24-27). Dipalmitoylphosphatidylcholine is used in thermo-sensitive liposomes for their ability to rupture on application and for their stability (C19, L36-39).

Regarding **claims 41, 43, and 44**, the limitations are disclosed above except for the monitoring of the compound being performed in real time. However, in the same field of endeavor Unger '935 teach the monitoring of the drug delivery and accumulation in real time (col. 35, lines 6-25). Therefore, it would have been obvious to a person of ordinary skill in the art at the time of the invention to monitor the liposome delivery in real time so that the operator can verify that the drug is being adequately delivered to the site of interest.

Regarding **claim 45**, by monitoring the release of the of the contrast agent, a temperature will be inherently reached by the thermosensitive liposome which would serve to release the contrast agent.

14. **Claims 5 and 21** are rejected under 35 U.S.C. 103(a) as being unpatentable over Lang '910 in view of Gamble et al. (U.S. 4,728,575). Lang '910 discloses all of the limitations as discussed above. Lang '910 does not

describe a liposome wherein the liposome comprises DSPC/Cholesterol. However, Gamble '575 teaches the use of a liposome comprising DSPC/Cholesterol (C4, L14). It would have been obvious to a person of ordinary skill in the art at the time of the invention to modify Lang '910 to use a lipid formulation of DSPC/Cholesterol as evidenced by Gamble '575. Such a modification would be advantageous in MRI contrast agent enhancement by promoting vesicle stability of the liposome that encapsulates the contrast agent (abstract).

Conclusion

15. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elmer Chao whose telephone number is (571)272-0674. The examiner can normally be reached on 9am-4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brian Casler can be reached on (571)272-4956. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Brian L Casler/
Supervisory Patent Examiner, Art Unit 3737

/E. C./
Examiner, Art Unit 3737
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